REMARKS

In the Office Action dated August 14, 2000 claims 1-20 are pending, claims 4-20 are withdrawn from consideration, and claims 1-3 are rejected. The rejection was made final.

The rejection under 35 U.S.C. § 112, first paragraph, was withdrawn.

Reference is made to the accompanying Declaration under 37 CFR §1.132 by Dr. James Clagett and the Declaration of Dr. John Lipani, which are being submitted along with this amendment.

Claims 1-2 are rejected under 35 U.S.C. 103(a), as obvious over Gleisner (*Inflammation* 5:13-17, 1981) in view of Oxford dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dumitrascu, and further in view of Kermode.

Claim 3 remains rejected under 35 U.S.C. 103 (a) for the reasons of record because the rejection of claims 1,2 is maintained.

For the sake of brevity, the rejections are addressed in combination. Such a combined response is considered appropriate because the rejection of claim 3 relies on the rejection of claims 1 and 2 based on a 103(a) rejection over Gleisner (*Inflammation* 5:13-17, 1981) in view of Oxford dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dumitrascu, and further in view of Kermode.

Each of the rejections is traversed.

Applicants claims 1, 2 and 3 are directed to a method for the treatment of an allergic reaction using f-Met-Leu-Phe-Phe. In the examples of the specification, applicants teach that f-Met-Leu-Phe-Phe has anti-inflammatory properties which include **inhibition** of mast cell degranulation (Example 1-11); **reduction** of adhesion,

migration and aggregation of lymphocytes, eosinophils and neutrophils to a site of inflammation (Example 12 and figures 8A-8C and 9A-9C); **reduction** of mucosal accumulation in the airways of the asthmatic mouse model (Example 12); **inhibition** of the release of histamines (Example 12); **inhibition** of the release of leukotrienes; wherein the inflammation is due to asthma, arthritis and anaphylaxis (Example 12). Applicants teach that the **anti-inflammatory** properties of f-Met-Leu-Phe-Phe are highly effective and are desirable for the treatment of such disorders.

Gleisner et al suggest that f-Met-Leu-Phe is an inhibitor of mast cell degranulation based on an experiment to analyze the increase of vascular permeability of the microcirculation of rat skin produced by 48/80, anti-rat IgE and PPF, the results of which are "are at best semiquantitative," (page 14 second sentence in the Results paragraph).

Most importantly, Gleisner ***fails*** to teach or suggest anything regarding the presently claimed method for treating an allergy reaction in a mammal comprising administering to the mammal an anti-allergic effective amount of **f-Met-Leu-Phe-Phe**.

The examiner cites Kermode [sic, reference AE], *Biochem. J.* (1991) **276**, as disclosing that formuyl Met peptides, such as f-Met-Leu-Phe, f-Met-Leu-Phe-Phe, and f-Met-Leu-Phe-Tyr are functional equivalents. However, contrary to the disclosure of Gleisner et al., Kermode et al. teach that formyl peptides, particularly, f-Met-Leu-Phe-Phe, stimulate the degranulation of neutrophils and chemotaxis. That is an inflammatory response and is **not** desirable for treating allergies.

Ferry et al. and Anderson et al. both teach that f-met peptides are inflammatory.

There is a significant and unexpected difference between the f-Met-Leu-Phe peptide, which activates the neutrophil, and the presently claimed **f-Met-Leu-Phe-**

Phe, which inhibits neutrophil activity. "The binding of these peptides to mast cells apparently prevents their activation (i.e., degranulation), whereas these same compounds activate the neutrophil," (see Gleisner, page 16, first sentence). Gleisner teaches that there is functional **variability** of f-Met-Leu-Phe action on different immune cells and it cannot be *prima facie* obvious that a formyl Met peptide variant, such as f-Met-Leu-Phe-Phe would have a mechanism of action as described in the present application, when Gleisner teaches that f-Met-Leu-Phe causes different immune cells to react differently, and Kermode teaches that f-met paeptides are equivalent..

The combination of Gleisner with Kermode **underscore** the variability of so-called "functional equivalents" of f-Met-Leu-Phe peptides. Kermode et al teach that chemotactic formyl Met peptides trigger biological responses of neutrophils which play a major role in the body's defense mechanism against infectious microorganisms. The reference teaches that f-Met-Leu-Phe-Phe binds to both high and low affinity receptors of neutrophils *in vitro*, is a powerful mediator of neutrophil degranulation as measured by β-glucosaminidase release *in vitro,* and is a potent chemotactic agent for neutrophils. The teachings of Kermode support the teachings of Gleisner that f-Met-Leu-Phe is a powerful activator of neutrophils.

On the contrary, Applicants teach that f-Met-Leu-Phe-Phe **inhibits** all of the above responses. Based on the properties of f-Met-Leu-Phe-Phe as described by Gleisner et al. and Kermode et al, it would not have been obvious to anyone skilled in the art, much less one of ordinary skill in the art, to use f-Met-Leu-Phe-Phe for the treatment of an allergic reaction, i.e., for **downregulation** of the inflammatory response.

Prior to the present discovery by Applicants, no one would have considered the use of f-met-leu-phe-phe to treat an allergic reaction. See the Declaration of Dr. Lipani, paragraph 19.

Casale and Dumitrascu teach that mast cells are extremely important mediators in the pathogenesis of asthma but do not teach or suggest methods of inhibiting mast cell activation. Furthermore, mast cells are not the only cells involved in the mechanisms of asthma. Neutrophils and other immune cells play an equally important role (page 21, lines 12-23 of the present specification) The teachings by Gleisner (that f-Met-Leu-Phe inhibits mast cell degranulation but remains a powerful chemotactic agent for mast cells), the combination of teachings by Gleisner and Kermode (that f-Met-Leu-Phe is a potent activator of neutrophils), and the teachings of Kermode (that f-Met-Leu-Phe-Phe is a powerful chemotactic agent for neutrophils) are powerful examples showing that these cells are recruited to a site of inflammation.

On the contrary, the present application surprisingly and unexpectedly teaches that f-Met-Leu-Phe-Phe has an inhibitory effect on **both** mast cells and neutrophils as f-Met-Leu-Phe-Phe **inhibits** inflammation at the **earliest stages** by inhibiting the recruitment of inflammatory cells to the site of inflammation.

Thus, the fact that Casale and Dumitrascu teach that mast cells are important in the mechanism of asthma does not make the present invention obvious.

The present application teaches that f-Met-Leu-Phe-Phe is a powerful inhibitor of the asthma allergic response due to its potent ability to inhibit mast cell degranulation **and** prevent inflammatory cells from infiltrating a site of inflammation.

The Oxford dictionary of Biochemistry and Molecular Biology (1981) teaches that antihistamines are used to treat allergic reactions. However, there is no teaching or suggestion that formyl Met peptides can act as antihistamines and based on the teachings of Gleisner and Kermode, as discussed above, it would not be anticipated that any formyl Met peptide would be effective as an antihistamine. Indeed, no present claim is made that f-Met-Leu-Phe-Phe is an antihistamine.

In Response to the Examiner's arguments regarding the Declaration filed 06/12/00, a new Declaration by Dr. Clagett is being submitted herewith. The declaration presents tests illustrating the effects of fMLP alone, and of HK-X (fMLPP) both alone and in conjunction with fMLP in the mouse model. The results of these experiments are surprising and unexpected in view of the prior art teachings for f-met peptides.

Briefly, in the experiments, there was subcutaneously injected into the dorsum of mice feet 200 µg of **fMLP** alone; 200 µg of HK-X (fMLPP) alone; 200 µg of fMLP and 200 µg of HK-X together; and as a control the vehicle (4% DMSO in Tyrode's solution).

The results showed that fMLP alone induced a potent chemotactic response. However, by itself, HK-X was **not** chemotactic and HK-X **inhibited** the chemotactic capacity of fMLP when HK-X and fMLP were administered together. Therefore, HK-X mechanism of action functions at the **earliest** stage of inflammation by **inhibiting** the recruitment of inflammatory cells. A second important property of HK-X is that it also **inhibits** the action of a potent chemotactic agent.

Accordingly, applicants respectfully submit that the combination of Gleisner, in view of Oxford dictionary of Biochemistry and Molecular Biology (1981) and Casale and Dumitrascu, and further in view of Kermode, does not teach or suggest the invention of claims 1-3 and, thus, the applicants request that this rejection be withdrawn.

Applicants respectfully submit that the rejection to claim 1-3 has been traversed, as discussed above, hence, placing claims 1-3 in a condition for allowance.

C

In view of the foregoing, applicants submit that all of the rejections set forth in the August 14, 2000 Office Action have been overcome, and that the case is in condition for allowance. Early and favorable action is requested.

Although it is believed that no further charges are required, please charge any additional necessary fees to Deposit Account No.: 04-1105.

Respectfully submitted,

DATE: 13 Jan '01

George W. Neuner (Reg. No. 26,964)
Attorney for Applicants

Dike, Bronstein, Roberts & Cushman
Intellectual Property Practice Group
EDWARDS & ANGELL, LLP
130 Water Street
Boston, MA 02109
TEL 617-523-3400
FAX 617-523-6440